

Heterocycles in Medicinal Chemistry III

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The rapid development of organic chemistry in the early 19th century also saw the development of heterocyclic chemistry [1]. Heterocyclic compounds are cyclic organic molecules in which one or more carbon atoms in the ring are replaced by a heteroatom [1–3]. The most common heteroatoms are nitrogen, oxygen, and sulfur [4,5]. However, other heteroatoms such as phosphorus and silicon can also occur, as well as more exotic heteroatoms such as selenium, arsenic, germanium, tin, antimony, tellurium, lead, or bismuth [6–8].

The basic classification of heterocycles is based on the heteroatoms and their number (monovalent, divalent and polyvalent), the ring size (5-, 6-, 7-, 8-membered) and the degree of their (un)saturation, i.e., saturated organic heterocycles behave as acyclic derivatives, while unsaturated ones, which meet the Hückel condition for aromaticity ($4n + 2$ π -electrons in the system, where $n \geq 0$), behave as aromatic systems. In a heterocycle, a heteroatom often contributes its lone electron pair to the aromatic π -system, depending on the type/number of heteroatoms and the ring size, nitrogen-containing heterocycles can be strongly basic, because the lone electron pair is not part of the aromatic sextet. A large class of organic so-called fused heterocycles is formed by combining a heterocycle with benzene or another aromatic heterocycle as illustrated in Figure 1. In addition to the “classical” organic heterocycles, there are also “rare” heterocycles that can be called inorganic because they do not contain any carbons in their structure; examples include cyclic borazine (B_3N_3), hexachlorophosphazene (P_3N_3), and trithiazyl trichloride (S_3N_3) [3–5,8–16].

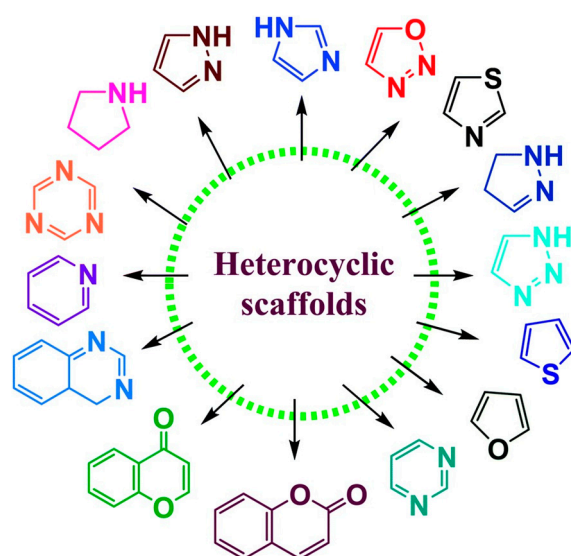


Figure 1. Various heterocyclic scaffolds. Adapted from [17]. Copyright 2020, Royal Society of Chemistry.

The nomenclature of heterocycles is as follows: (i) trivial—the oldest and used mainly for five- and six-membered heterocycles and their derivatives; (ii) replacement/substitution—



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derived from the name of the carbocycle by replacing the carbon atom with a prefix indicating the heteroatom, e.g., aza, oxa, and thia; and (iii) the universal Hantzsch-Widman system—allowing the creation of names for 3- to 10-membered heterocycles using prefixes for heteroatoms and a stem expressing the number of members and the saturation of the cycle [3–5,8].

Essentially, any carbocyclic compound, regardless of structure and functionalization, can in principle be converted into a set of heterocyclic isosteres/analogues by replacing one or more carbon atoms in the ring with another element [3–5,8,18]. Organic heterocycles thus constitute the largest and most diverse group of organic compounds with a wide range of uses/applications; see Figure 2. This diversity is achieved by varying the presence and number of heteroatoms, their position/arrangement of these heteroatoms, and aromaticity [19–23]. For example, >85% of bioactive compounds contain at least one nitrogen atom in their structure [24–29] and >75% of heterocyclic clinically used drugs contain at least two heteroatoms [20–22,30], with the most commonly used building blocks being triazoles, tetrazoles, imidazoles/benzimidazoles/benzothiazoles, pyrimidines, and azanaphthalenes [1,2,31–45].

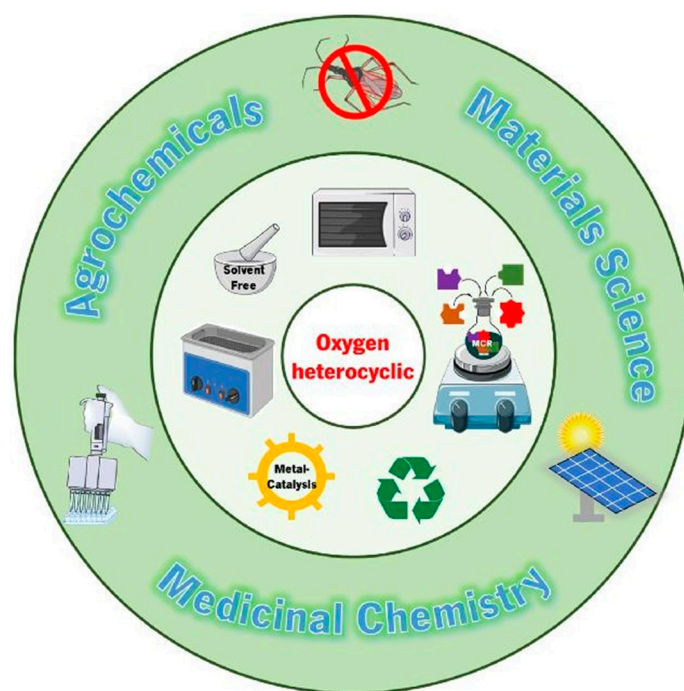


Figure 2. Methods of preparation and use of heterocycles. Modified by [46]. Copyright 2026, MDPI.

Differences in the structure of bioactive heterocycles have a significant impact on the physicochemical properties and the possibilities of construction/synthesis of heterocyclic systems [47–53]. In addition, heterocycles can be further functionalized to further modify/optimize their properties and, in the case of bioactive compounds (drug candidates), their bioavailability can be influenced (to achieve the most favourable ADME/Tox profile) [51,54–58]. Bioisosteric replacement of functional groups with heterocyclic fragments can optimize the efficacy and selectivity [53,59–63]. It should be mentioned that many natural substances (including secondary metabolites) are composed of heterocycles and many heterocyclic systems (nucleic acids, carbohydrates, and proteins) are essential for life [2,64–66]. Heterocyclic compounds have attracted much attention due to their numerous important biological effects, whether as agrochemicals (pesticides, herbicides, and growth-promoting molecules) [23,67–75] or as pharmaceutically important compounds (human or veterinary drugs or as drug carriers) [1,2,76–83]. Many natural heterocyclic

biomolecules of plant, microbial or animal origin have served as a source of inspiration (model compounds) for the subsequent development of synthetic modifications that have become drugs. Heterocycles are found in more than 90% of new drugs and often form the basic scaffold [20,21,29,84]. Their structural diversity and versatility make them attractive building blocks for drug design.

Heterocyclic compounds are found in all classes of drugs [20,21,76–78,85] or agrochemicals [23,67–73]. They have antibacterial, antifungal, antiviral, antiparasitic, anthelmintic effects, are used as antineoplastics, antiemetics, antipyretics, antihistamines/antiallergics, have anti-inflammatory, antioxidant, anticonvulsant, antihypertensive and antihyperlipidemic activities, and all drugs that affect the central nervous system in any way (i.e., antipsychotics, antiepileptics, antiparkinsonians, anxiolytics, antidepressants, and hypnotics/sedatives) are also heterocyclic [20,21,24,32–34,37–45,76–78,84–87].

This Special Issue, which contains nine research articles and four review papers, aims to highlight some of the recent advances in the exciting field of heterocyclic chemistry by gathering the latest findings from research on bioactive heterocyclic compounds.

Four review articles discuss new synthetic approaches (contribution 1), analyze the benefits of natural triazole and pyrazole derivatives as potential compounds for cancer treatment (contribution 2), discuss versatile therapeutic applications (contribution 3), and even the modern reuse of heterocycles in pharmaceuticals (contribution 4). In recent years, advances in the synthesis and rational design of new drugs resulted in the optimization of heterocyclic compounds with enhanced biological activity due to a deeper understanding of structure–activity relationships. Examples include nitrogen-containing heterocyclic multifunctional compounds with the potential to control plant pathogens (contribution 5), pyrroloquinolines (contribution 6), indenoquinolines (contribution 7), quinolines (contribution 8) as potential antineoplastic drugs, or quinazolines (contribution 9) with neuroprotective potential. Chromone derivatives (contribution 10) and phenoxazine (contribution 11) expressed antifungal activity. On the other hand, thiazoles have been proposed as oxidative stress neutralizers (contribution 12) or tyrosinase inhibitors (contribution 13).

It can be stated that the synergy between medicinal chemists, pharmacologists and computer scientists has significantly accelerated the development of new drugs based on heterocyclic scaffolds. The use of advanced technologies allows scientists to overcome the limits of molecular design, opening the way to new therapeutic strategies. Heterocycles thus represent a key tool of modern medicine in the search for drugs for pathologies that are still difficult to treat.

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List of Contributions

1. Keydel, T.; Link, A. Synthetic approaches, properties, and applications of acylals in preparative and medicinal chemistry. *Molecules* **2024**, *29*, 4451. <https://doi.org/10.3390/molecules29184451>.
2. Fermo, A.D.; Bisi, A.; Orioli, R.; Gobbi, S.; Belluti, F. Triazole and pyrazole hybrids of electrophilic natural products as promising anticancer agents. *Molecules* **2026**, *31*, 355. <https://doi.org/10.3390/molecules31020355>.
3. Mo, X.; Rao, D.P.; Kaur, K.; Hassan, R.; Abdel-Samea, A.S.; Farhan, S.M.; Brase, S.; Hashem, H. Indole derivatives: A versatile scaffold in modern drug discovery—An updated review on their multifaceted therapeutic applications (2020–2024). *Molecules* **2024**, *29*, 4770. <https://doi.org/10.3390/molecules29194770>.

4. Zolotareva, D.; Zazybin, A.; Belyankova, Y.; Bayazit, S.; Dauletbakov, A.; Seilkhanov, T.; Kemelbekov, U.; Aydemir, M. Heterocyclic antidepressants with antimicrobial and fungicide activity. *Molecules* **2025**, *30*, 1102. <https://doi.org/10.3390/molecules30051102>.
5. Szlauzys, M.; Ostrowski, K.; Nowak, D.; Prukała, W.; Starzyk, J.; Jasiewicz, B.; Mrowczyńska, L. Hybrid uracil derivatives with caffeine and gramine obtained via click chemistry as potential antioxidants and inhibitors of plant pathogens. *Molecules* **2025**, *30*, 2714. <https://doi.org/10.3390/molecules30132714>.
6. Kroger, L.; Borgert, S.; Lauwers, M.; Steinkrüger, M.; Jose, J.; Pietsch, M.; Wunsch, B. Structure–activity relationship studies of tetracyclic pyrrolocarbazoles inhibiting heterotetrameric protein kinase CK2. *Molecules* **2025**, *30*, 63. <https://doi.org/10.3390/molecules30010063>.
7. Rodriguez-Paniagua, A.; Tesauro, C.; Knudsen, B.R.; Fuertes, M.; Alonso, C. Phosphine oxide indenoquinoline derivatives: synthesis and biological evaluation as topoisomerase I inhibitors and antiproliferative agents. *Molecules* **2024**, *29*, 5992. <https://doi.org/10.3390/molecules29245992>.
8. Zieba, A.; Pindjakova, D.; Latocha, M.; Plonka-Czerw, J.; Kusmierz, D.; Cizek, A.; Jampilek, J. Design, synthesis, and anticancer and antibacterial activities of quinoline-5-sulfonamides. *Molecules* **2024**, *29*, 4044. <https://doi.org/10.3390/molecules29174044>.
9. Laversin, A.; Dufosse, R.; Bolteau, R.; Duroux, R.; Ravez, S.; Hernandez-Tapia, S.; Fossart, M.; Coevoet, M.; Liberelle, M.; Yous, S.; et al. Novel quinazoline derivatives as highly effective $\alpha 2\alpha$ adenosine receptor antagonists. *Molecules* **2024**, *29*, 3847. <https://doi.org/10.3390/molecules29163847>.
10. Bonvicini, F.; Menegaldo, L.; Orioli, R.; Belluti, F.; Gentilomi, G.A.; Gobbi, S.; Bisi, A. Extended antimicrobial profile of chromone–butenafine hybrids. *Molecules* **2025**, *30*, 2973. <https://doi.org/10.3390/molecules30142973>.
11. Pacheco, M.I.; Guimarães, B.; Pereira-Silva, P.; Costa-Barbosa, A.; Gonçalves, M.S.T.; Sousa, M.J.; Sampaio, P. Combining fluconazole with benzo[a]phenoxazine derivatives as a promising strategy against fluconazole-resistant *Candida* species. *Molecules* **2024**, *29*, 5197. <https://doi.org/10.3390/molecules29215197>.
12. Cornea, A.C.; Marc, G.; Ionuț, I.; Moldovan, C.; Stana, A.; Oniga, S.D.; Pirnau, A.; Vlase, L.; Oniga, I.; Oniga, O. Synthesis, characterization, and antioxidant activity evaluation of new *N*-methyl substituted thiazole-derived polyphenolic compounds. *Molecules* **2025**, *30*, 1345. <https://doi.org/10.3390/molecules30061345>.
13. Park, H.S.; Jung, H.J.; Park, H.S.; Kim, H.J.; Noh, S.G.; Park, Y.; Chun, P.; Chung, H.Y.; Moon, H.R. Design and synthesis of novel 6-(substituted phenyl)-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*]thiazole compounds as tyrosinase inhibitors: In vitro and in vivo insights. *Molecules* **2025**, *30*, 1535. <https://doi.org/10.3390/molecules30071535>.

References

1. Seema, K.; Shruti, K.; Sakshi, K.; Tejashree, K.; Supriya, S. The importance of heterocycles in drug discovery: From biological activity to pharmaceutical applications. *Int. J. Sci. Res. Technol.* **2025**, *2*, 55–64. [CrossRef]
2. Kabir, E.; Uzzaman, M. A review on biological and medicinal impact of heterocyclic compounds. *Results Chem.* **2022**, *4*, 100606. [CrossRef]
3. Virtual Textbook of Organic Chemistry-Heterocyclic Compounds. Available online: <https://www2.chemistry.msu.edu/faculty/reusch/virttxtjml/heterocy.htm> (accessed on 23 January 2026).
4. Joule, J.A.; Mills, K. *Heterocyclic Chemistry*; Wiley-Blackwell: Chichester, UK, 2010.
5. Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, Germany, 2012.
6. Rousseau, G.; Blanco, L. Heterocyclic compounds with a silicon atom and another non-adjacent different heteroatom. *Tetrahedron* **2006**, *62*, 7951–7993. [CrossRef]
7. Kumar, R.; Dohi, T.; Zhdankin, V.V. Organohypervalent heterocycles. *Chem. Soc. Rev.* **2024**, *53*, 4786–4827. [CrossRef] [PubMed]
8. Katritzky, A.R.; Denisko, O.V. “Heterocyclic Compound”. Encyclopedia Britannica. Available online: <https://www.britannica.com/science/heterocyclic-compound> (accessed on 23 January 2026).
9. Chivers, T.; Laitinen, R.S. Insights into the formation of inorganic heterocycles via cyclocondensation of primary amines with group 15 and 16 halides. *Dalton Trans.* **2017**, *46*, 1357–1367. [CrossRef]
10. Volkov, V.V.; Myakishev, K.G.; Ilinchik, E.A. Borazine and its derivatives: Synthesis, mechanochemical synthesis reactions and outlooks for technological applications. *Chem. Sustain. Dev.* **2009**, *17*, 225–234.

11. Edin, S.; Sandoval-Pauker, C.; Yutronkie, N.J.; Takacs, Z.; Wilhelm, F.; Rogalev, A.; Pinter, B.; Pedersen, K.S.; Reinholdt, A. Unleashing phosphorus mononitride. *Nat. Commun.* **2025**, *16*, 5596. [\[CrossRef\]](#)
12. Higham, L.J.; Allen, D.W. *Organophosphorus Chemistry*; Royal Society of Chemistry: Croydon, UK, 2024; Volume 52.
13. Yildiz Gul, E.; Tiryaki, B.; Kose, B.; Ozturk, N.; Okutan, E.; Dedeoglu, B.; Tanriverdi Ecik, E. Design, synthesis and in vitro evaluations of new cyclotriphosphazenes as safe drug candidates. *RSC Med. Chem.* **2025**, *16*, 2061–2077. [\[CrossRef\]](#)
14. Zibarov, A.; Oukhrib, A.; Aujard Catot, J.; Turrin, C.O.; Caminade, A.M. AB₅ Derivatives of cyclotriphosphazene for the synthesis of dendrons and their applications. *Molecules* **2021**, *26*, 4017. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Passmore, J.; Schriver, M.J. Investigation into the nature and chemistry of thiazyl chloride monomer and trimer (NSCL)_n (n = 1,3) in solution using nitrogen-14 NMR spectroscopy, a useful routine tool for the characterization of small sulfur-nitrogen-containing compounds. *Inorg. Chem.* **1988**, *27*, 2749–2751. [\[CrossRef\]](#)
16. Duan, X.G.; Duan, X.L.; Rees, C.W.; Yue, T.Y. Organic chemistry of trithiazyl trichloride. *J. Het. Chem.* **1996**, *33*, 1419–1427. [\[CrossRef\]](#)
17. Obaid, R.J.; Naeem, N.; Mughal, E.U.; Al-Rooqi, M.M.; Sadiq, A.; Jassas, R.S.; Moussa, Z.; Ahmed, S.A. Inhibitory potential of nitrogen, oxygen and sulfur containing heterocyclic scaffolds against acetylcholinesterase and butyrylcholinesterase. *RSC Adv.* **2022**, *12*, 19764. [\[CrossRef\]](#)
18. Sharma, R.; Arisawa, M.; Takizawa, S.; Salem, M.S.H. Remodelling molecular frameworks via atom-level surgery: Recent advances in skeletal editing of (hetero)cycles. *Org. Chem. Front.* **2025**, *12*, 1633–1670. [\[CrossRef\]](#)
19. Favi, G. Modern strategies for heterocycle synthesis. *Molecules* **2020**, *25*, 2476. [\[CrossRef\]](#)
20. Vitaku, E.; Smith, D.T.; Njardarson, J.T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274. [\[CrossRef\]](#) [\[PubMed\]](#)
21. Marshall, C.M.; Federice, J.G.; Bell, C.N.; Cox, P.B.; Njardarson, J.T. An update on the nitrogen heterocycle compositions and properties of U.S. FDA-approved pharmaceuticals (2013–2023). *J. Med. Chem.* **2024**, *67*, 11622–11655. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Li Petri, G.; Holl, R.; Spano, V.; Barreca, M.; Sardo, I.; Raimondi, M.V. Emerging heterocycles as bioactive compounds. *Front. Chem.* **2023**, *11*, 1202192. [\[CrossRef\]](#)
23. Lamberth, C. Isosteric ring exchange as a useful scaffold hopping tool in agrochemistry. *J. Agric. Food Chem.* **2023**, *71*, 18123–18132. [\[CrossRef\]](#)
24. Heravi, M.M.; Zadsirjan, V. Prescribed drugs containing nitrogen heterocycles: An overview. *RSC Adv.* **2020**, *10*, 44247–44311. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Kumari, S.; Carmona, A.V.; Tiwari, A.K.; Trippier, P.C. Amide bond bioisosteres: Strategies, synthesis, and successes. *J. Med. Chem.* **2020**, *63*, 12290–12358. [\[CrossRef\]](#)
26. La Monica, G.; Bono, A.; Alamia, F.; Lauria, A.; Martorana, A. Bioisosteric heterocyclic analogues of natural bioactive flavonoids by scaffold-hopping approaches: State-of-the-art and perspectives in medicinal chemistry. *Bioorg. Med. Chem.* **2024**, *109*, 117791. [\[CrossRef\]](#)
27. Ballatore, C.; Huryn, D.M.; Smith, A.B. Carboxylic acid (bio)isosteres in drug design. *ChemMedChem* **2013**, *8*, 385–395. [\[CrossRef\]](#)
28. Bredael, K.; Geurs, S.; Clarisse, D.; De Bosscher, K.; D’Hooghe, M. Carboxylic acid bioisosteres in medicinal chemistry: Synthesis and properties. *J. Chem.* **2022**, *2022*, 2164558. [\[CrossRef\]](#)
29. Qadir, T.; Amin, A.; Kumar Sharma, P.; Jeelani, I.; Abe, H. A review on medicinally important heterocyclic compounds. *Open Med. Chem. J.* **2022**, *16*, e187410452202280. [\[CrossRef\]](#)
30. Sharma, S.; Kumar, D.; Singh, G.; Monga, V.; Kumar, B. Recent advancements in the development of heterocyclic anti-inflammatory agents. *Eur. J. Med. Chem.* **2020**, *200*, 112438. [\[CrossRef\]](#) [\[PubMed\]](#)
31. Pibiri, I. Recent advances: Heterocycles in drugs and drug discovery. *Int. J. Mol. Sci.* **2024**, *25*, 9503. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Brase, S. *Privileged Scaffolds in Medicinal Chemistry: Design, Synthesis, Evaluation*; RSC Publishing: London, UK, 2015.
33. Skorenski, M.; Sienczyk, M. The Fellowship of privileged scaffolds—One structure to inhibit them all. *Pharmaceuticals* **2021**, *14*, 1164. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Yu, B.; Li, N.; Fu, C. *Privileged Scaffolds in Drug Discovery*; Academic Press & Elsevier: London, UK, 2023.
35. Frank, E.; Szollosi, G. Nitrogen-containing heterocycles as significant molecular scaffolds for medicinal and other applications. *Molecules* **2021**, *26*, 4617. [\[CrossRef\]](#)
36. Ebenezer, O.; Jordaan, M.A.; Carena, G.; Bono, T.; Shapi, M.; Tuszyński, J.A. An overview of the biological evaluation of selected nitrogen-containing heterocycle medicinal chemistry compounds. *Int. J. Mol. Sci.* **2022**, *23*, 8117. [\[CrossRef\]](#)
37. Nitulescu, G.M. Quantitative and qualitative analysis of the anti-proliferative potential of the pyrazole scaffold in the design of anticancer agents. *Molecules* **2022**, *27*, 3300. [\[CrossRef\]](#)
38. Murtazaeva, Z.; Nasrullaev, A.; Buronov, A.; Gaybullaev, S.; Nie, L.; Numonov, S.; Khushnazarov, Z.; Turgunov, D.; Kuryazov, R.; Zhao, J.; et al. Imidazole hybrids: A privileged class of heterocycles in medicinal chemistry with new insights into anticancer activity. *Molecules* **2025**, *30*, 2245. [\[CrossRef\]](#)

39. Imramovsky, A.; Pejchal, V.; Stepankova, S.; Vorcakova, K.; Jampilek, J.; Vanco, J.; Simunek, P.; Kralovec, K.; Bruckova, L.; Mandikova, J.; et al. Synthesis and in vitro evaluation of new derivatives of 2-substituted-6-fluorobenzo[d]thiazoles as cholinesterase inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 1735–1748. [CrossRef] [PubMed]
40. Polanski, J.; Kurczyk, A.; Bak, A.; Musiol, R. Privileged structures—Dream or reality: Preferential organization of azanaphthalene scaffold. *Curr. Med. Chem.* **2012**, *19*, 1921–1945. [CrossRef]
41. Musiol, R. An overview of quinoline as a privileged scaffold in cancer drug discovery. *Expert Opin. Drug Discov.* **2017**, *12*, 583–597. [CrossRef] [PubMed]
42. Jampilek, J.; Dolezal, M.; Opletalova, V.; Hartl, J. 5-Lipoxygenase, leukotrienes biosynthesis and potential antileukotrienic agents. *Curr. Med. Chem.* **2006**, *13*, 117–129. [CrossRef]
43. Musiol, R.; Jampilek, J.; Nycz, J.E.; Pesko, M.; Carroll, J.; Kralova, K.; Vejsova, M.; O'Mahony, J.; Coffey, A.; Mrozek, A.; et al. Investigating the activity spectrum for ring-substituted 8-hydroxyquinolines. *Molecules* **2010**, *15*, 288–304. [CrossRef] [PubMed]
44. Mrozek-Wilczkiewicz, A.; Kalinowski, D.S.; Musiol, R.; Finster, J.; Szurko, A.; Serafin, K.; Knas, M.; Kamalapuram, S.K.; Kovacevic, Z.; Jampilek, J.; et al. Investigating the anti-proliferative activity of styrylzanaphthalenes and azanaphthalenediones. *Bioorg. Med. Chem.* **2010**, *18*, 2664–2671. [CrossRef]
45. Kos, J.; Ku, C.F.; Kapustikova, I.; Oravec, M.; Zhang, H.; Jampilek, J. 8-Hydroxyquinoline-2-carboxanilides as antiviral agents against avian influenza virus. *ChemistrySelect* **2019**, *4*, 4582–4587. [CrossRef]
46. Proenca, F.; Marinho, E.M.R. Oxygen-containing heterocyclic compounds: Recent advances in chemistry. *Chemistry* **2026**. Available online: https://www.mdpi.com/journal/chemistry/special_issues/7H8DM320B9 (accessed on 23 January 2026).
47. De, S.K. *Applied Organic Chemistry: Reaction Mechanisms and Experimental Procedures in Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2021.
48. Taylor, A.P.; Robinson, R.P.; Fobian, Y.M.; Blakemore, D.C.; Jones, L.H.; Fadeyi, O. Modern advances in heterocyclic chemistry in drug discovery. *Org. Biomol. Chem.* **2016**, *14*, 6611–6637. [CrossRef]
49. Budnikov, A.S.; Krylov, I.B.; Mulina, O.M.; Lapshin, D.A.; Terentev, A.O. CH-Functionalization of heterocycles with the formation of C–O, C–N, C–S/Se, and C–P bonds by intermolecular addition of heteroatom-centered radicals. *Adv. Synth. Catal.* **2023**, *365*, 1714–1755. [CrossRef]
50. Sivaraja, N.; Sakthivela, K.; Kikushima, K.; Kostic, M.D.; Dohi, T.; Singh, F.V. Recent advances in non-conventional synthesis of N-heterocyclic compounds: Emerging strategies and biological perspectives. *RSC Adv.* **2025**, *15*, 35509–35531. [CrossRef]
51. Rotella, D.P. Heterocycles in drug discovery: Properties and preparation. In *Advances in Heterocyclic Chemistry*; Meanwell, N.A., Lolli, M.L., Eds.; Academic Press & Elsevier: Cambridge, MA, USA, 2021; pp. 149–183.
52. Di Martino, S.; Amico, P.; De Rosa, M. Applications of bridgehead heterocycles in drug design and medicinal chemistry. *Top. Curr. Chem.* **2025**, *383*, 16. [CrossRef]
53. Nadal Rodriguez, P.; Ghashghaei, O.; Bagan, A.; Escolano, C.; Lavilla, R. Heterocycle-based multicomponent reactions in drug discovery: From hit finding to rational design. *Biomedicines* **2022**, *10*, 1488. [CrossRef]
54. Culen, M.; Rezacova, A.; Jampilek, J.; Dohnal, J. Designing a dynamic dissolution method: A review of instrumental options and corresponding physiology of stomach and small intestine. *J. Pharm. Sci.* **2013**, *102*, 2995–3017. [CrossRef]
55. Dalvie, D.; Kang, P.; Loi, C.M.; Goulet, L.; Nair, S. Influence of heteroaromatic rings on ADME properties of drugs check access. In *Metabolism, Pharmacokinetics and Toxicity of Functional Groups: Impact of the Building Blocks of Medicinal Chemistry on ADMET*; Smith, D.A., Ed.; RSC Publishing: London, UK, 2010; pp. 328–369.
56. Abbaoui, Z.; Khibech, O.; Karci, H.; Alghibawi, M. Synthesis, characterization, and anticancer evaluation of N-heterocyclic entities: ADME profiling and in silico predictions. *Toxicol. Rep.* **2026**, *16*, 102184. [CrossRef]
57. Jednacak, T.; Stepanic, V.; Habinovec, I.; Mikulandra, I.; Smokrovic, K.; Cipic Paljetak, H.; Bukvic, M.; Parlov Vukovic, J.; Grgicevic, I.; Divjak, L.; et al. Anti-infective macrozones: Design, biological evaluation and structure-activity relationships. *ADMET DMPK* **2026**, *14*, 3139. [CrossRef]
58. Venkataraman, M.; Rao, G.C.; Madavareddi, J.K.; Maddi, S.R. Leveraging machine learning models in evaluating ADMET properties for drug discovery and development. *ADMET DMPK* **2025**, *13*, 2772. [CrossRef] [PubMed]
59. Poulie, C.B.; Bunch, L. Heterocycles as nonclassical bioisosteres of α -amino acids. *ChemMedChem* **2013**, *8*, 205–215. [CrossRef] [PubMed]
60. Karthikeyan, S.; Grishina, M.; Kandasamy, S.; Mangaiyarkarasi, R.; Ramamoorthi, A.; Chinnathambi, S.; Pandian, G.N.; Kennedy, J.L. A review on medicinally important heterocyclic compounds and importance of biophysical approach of underlying the insight mechanism in biological environment. *J. Biomol. Struct. Dyn.* **2023**, *41*, 14599–14619. [CrossRef]
61. Natho, P.; Colella, M.; Luisi, R. Strained spiro heterocycles as potential bioisosteres: An update on the synthesis of heteroatom-containing spiro[2.3]hexanes and spiro[3.3]heptanes. *Chem. Commun.* **2025**, *61*, 6579–6594. [CrossRef] [PubMed]
62. Cruz, N. Drug design: Influence of heterocyclic structure as bioisosteres. *J. Med. Org. Chem.* **2022**, *5*, 113–117.
63. Martis, G.J.; Mugali, P.S.; Gaonkar, S.L. Recent progress in the synthesis, functionalization, and biological outlook of pyrimidines. *ACS Omega* **2025**, *10*, 46248–46271. [CrossRef] [PubMed]

64. Dewick, P.M. *Medicinal Natural Products: A Biosynthetic Approach*, 3rd ed.; John Wiley & Sons: Chichester, UK, 2009.
65. Shah, B.; Seth, A.K. *Textbook of Pharmacognosy and Phytochemistry*; Elsevier: New Delhi, India, 2010.
66. Osbourn, A.E.; Lanzotti, V. *Plant-Derived Natural Products: Synthesis, Function, and Application*; Springer Science + Business Media: New York, NY, USA, 2009.
67. Melnikov, N.N. *Chemistry of Pesticides*; Gunther, F.A., Gunther, J.D., Eds.; Springer: New York, NY, USA, 1971.
68. Lamberth, C. Heterocyclic chemistry in crop protection. *Pest. Manag. Sci.* **2013**, *69*, 1106–1114. [CrossRef]
69. FRAC Code List[®]. 2025. Available online: <https://www.frac.info/media/ljsi3qrv/frac-code-list-2025.pdf> (accessed on 23 January 2026).
70. Amin, A.; Qadir, T.; Kumar Sharma, P.; Jeelani, I.; Abe, H. A review on the medicinal and industrial applications of N-containing heterocycles. *Open Med. Chem. J.* **2022**, *16*, e187410452209010. [CrossRef]
71. Wu, X.; Yang, Z.; Bu, M.; Duan, J.; Zhang, A. Design, synthesis and bioactivity evaluation of heterocycle-containing mono- and bisphosphonic acid compounds. *Molecules* **2023**, *28*, 7509. [CrossRef]
72. Kulkarni, S.; Akolkar, H.; Khedkar, V.M.; Haghi, A.K. *S-Heterocycles: Retrospect, Prospects, and Biological Applications*; RSC Publishing: London, UK, 2024.
73. Quiroga, D.; Rodriguez, D.; Coy-Barrera, E. Recent advances in the synthesis and applications of 1,2,3/1,2,5-thiadiazole- and benzo[c][1,2,5/1,2,3]thiadiazole-type compounds. *Molecules* **2025**, *30*, 4373. [CrossRef] [PubMed]
74. El Sabagh, A.; Islam, M.S.; Hossain, A.; Iqbal, M.A.; Mubeen, M.; Waleed, M.; Reginato, M.; Battaglia, M.; Ahmed, S.; Rehman, A.; et al. Phytohormones as growth regulators during abiotic stress tolerance in plants. *Front. Agron.* **2022**, *4*, 765068. [CrossRef]
75. Zheng, Y.; Wang, X.; Cui, X.; Wang, K.; Wang, Y.; He, Y. Phytohormones regulate the abiotic stress: An overview of physiological, biochemical, and molecular responses in horticultural crops. *Front. Plant. Sci.* **2023**, *13*, 1095363. [CrossRef]
76. Wermuth, C.G.; Aldous, D.; Raboisson, P.; Rognan, D. *The Practice of Medicinal Chemistry*, 4th ed.; Academic Press & Elsevier: Oxford, UK, 2015.
77. Harrold, M.W.; Beck, K.; Roche, V.F.; Zito, S.W.; Lemke, T.L.; Williams, D.A. *Foye's Principles of Medicinal Chemistry*, 9th ed.; Lippincott Williams & Wilkins, Wolters Kluwer: Baltimore, MD, USA, 2025.
78. Brunton, L.L.; Knollman, B.C. *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, 14th ed.; McGraw Hill Medical: New York, NY, USA, 2023.
79. Alajely, M.S. Polymer and heterocyclic compounds their utility and application as drug. *Open Access J. Sci.* **2019**, *3*, 41–45. [CrossRef]
80. Duskey, J.T.; Baraldi, C.; Gamberini, M.C.; Ottonelli, I.; Da Ros, F.; Tosi, G.; Forni, F.; Vandelli, M.A.; Ruozi, B. Investigating novel syntheses of a series of unique hybrid PLGA-chitosan polymers for potential therapeutic delivery applications. *Polymers* **2020**, *12*, 823. [CrossRef]
81. Pontillo, A.R.N.; Konstanteli, E.; Bairaktari, M.M.; Detsi, A. Encapsulation of the natural product tyrosol in carbohydrate nanosystems and study of their binding with ctDNA. *Polymers* **2021**, *13*, 87. [CrossRef] [PubMed]
82. Alsolami, E.S.; Alorfi, H.S.; Alamry, K.A.; Hussein, M.A. One-pot multicomponent polymerization towards heterocyclic polymers: A mini review. *RSC Adv.* **2024**, *14*, 1757–1781. [CrossRef] [PubMed]
83. Li, T.T.; Zong, Y.; Chen, Z.; Luo, J.; Liu, N.; Wu, Z.Q. Helical polymers as drug delivery carriers. *Chem. Asian J.* **2025**, *20*, e202401635. [CrossRef] [PubMed]
84. Ahmad, G.; Sohail, M.; Bilal, M.; Rasool, N.; Qamar, M.U.; Ciurea, C.; Marceanu, L.G.; Misarca, C. N-Heterocycles as promising antiviral agents: A comprehensive overview. *Molecules* **2024**, *29*, 2232. [CrossRef]
85. Ward, M.; O'Boyle, N.M. Analysis of the structural diversity of heterocycles amongst European Medicines Agency approved pharmaceuticals (2014–2023). *RSC Med. Chem.* **2025**, *16*, 4540–4570. [CrossRef]
86. Musiol, R.; Kowalczyk, W. Azole antimycotics—A highway to new drugs or a dead end? *Curr. Med. Chem.* **2012**, *19*, 1378–1388. [CrossRef]
87. Musiol, R.; Malecki, P.; Pacholczyk, M.; Mularski, J. Terpyridines as promising antitumor agents: An overview of their discovery and development. *Expert Opin. Drug Discov.* **2022**, *17*, 259–271. [CrossRef]

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